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## EUROPEAN PATENT APPLICATION

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④ 17Beta-(cyclopropylamino)androst-5-EN-3beta-ol and related compounds useful as C17-20 lyase inhibitors.

⑦ This invention is directed to 17 $\beta$ -(cyclopropylamino)androst-5-en-3 $\beta$ -ol and related compounds and also to a method for using such compounds in the treatment of androgen-dependent disorders. The compounds are prepared by the hydride reduction of an appropriate steroidal imine or enamine.

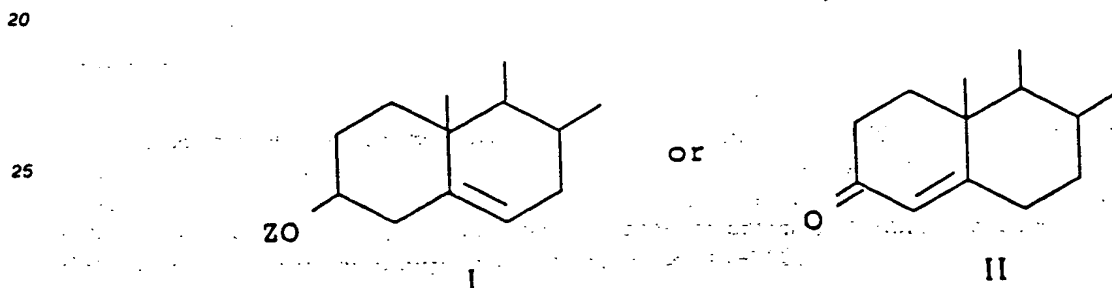
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# 17 $\beta$ -(CYCLOPROPYLAMINO)ANDROST-5-EN-3 $\beta$ -OL AND RELATED COMPOUNDS USEFUL AS C<sub>17</sub> 2 $\alpha$ LYASE INHIBITORS

The present invention is directed to 17 $\beta$ -(cyclopropylamino) androst-5-en-3 $\beta$ -ol and related compounds and also to a method for using such compounds in the treatment of androgen-dependent disorders. More particularly, the present invention is directed to a group of compounds having the following general formula:



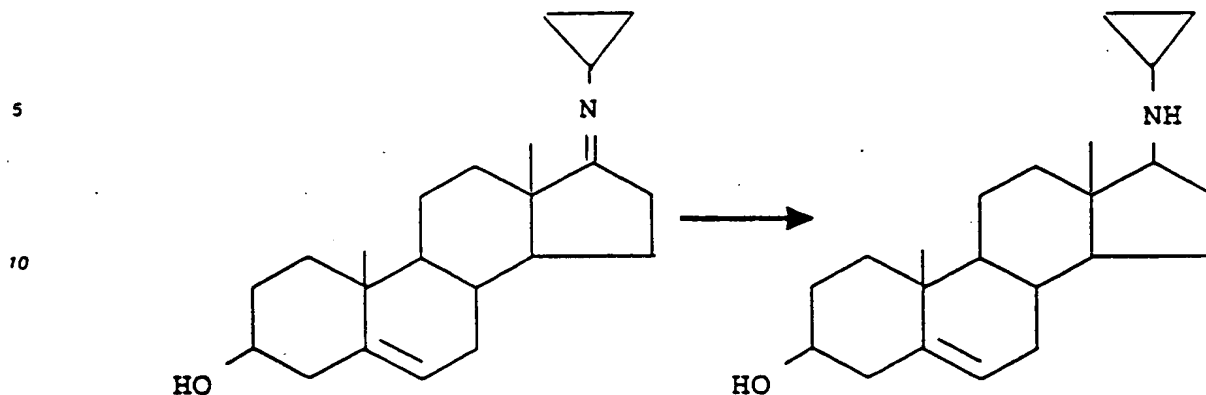
wherein R is hydrogen or methyl; R' is hydrogen, C<sub>1</sub> C<sub>4</sub> alkyl or cyclopropyl; and Q is



wherein Z is hydrogen, alkanoyl of 1-10 carbon atoms or cyclopentane- and benzene-alkanoyl wherein the alkanoyl portion contains up to 4 carbon atoms. Examples of alkanoyl group are acetyl, propionyl, butanoyl, and decanoyl; examples of the cyclopentane- and benzene-alkanoyl groups are cyclopentanepropionyl and benzenepropionyl. Preferred compounds are those in which Q is structure I.

Acid addition salts of the aforesaid compounds with pharmaceutically acceptable acids are equivalent to the above amines for the purposes of this invention. Illustrative of such salts are the salts with inorganic acids such as, for example, hydrochloric, hydrobromic, sulfuric, phosphoric and like acids; with organic carboxylic acids such as, for examples, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic and dihydroxymaleic, benzoic, phenylacetic, 4-aminobenzoic, 4-hydroxybenzoic, anthranilic, cinnamic, salicylic, 4-aminosalicylic, 2-phenoxybenzoic, 2-acetoxybenzoic, mandelic and like acids; and with organic sulfonic acids such as methanesulfonic acid and p-toluenesulfonic acids.

The compounds of the present invention are conveniently prepared by the reduction of an appropriate steroidal imine or enamine, wherein the compound used is a 3-hydroxy or 3-alkanoylhydroxy- $\Delta^5$ -steroid, with a hydride reducing agent. Where the starting material is an imine, the reaction can be illustrated as follows:



In this case, the reduction is carried out using a hydride reducing agent, preferably sodium borohydride, in an alkanol solvent. Prior to carrying out the reduction shown above, the steroid starting material can be acylated using, for example, acetic anhydride to give the corresponding 3-acetoxy steroid which is then reduced with borohydride as described earlier to give the corresponding 3-acetoxy product. In either case, the product obtained is a secondary amine which can be converted to the corresponding N-methyl compound by treatment with formaldehyde and formic acid in an Eschweiler-Clarke reaction or by reaction with aqueous formaldehyde and sodium borohydride.

Those compounds wherein R' is C<sub>2</sub> & alkyl can be obtained from a 17-cyclopropylamino steroid. This is reacted, for example, with acetyl chloride to give the corresponding acetamide which is then reduced with sodium cyanoborohydride to give the N-ethyl compound. In those cases where the above reaction with acetyl chloride also gives the 3-ester, the ester group can be removed, after the reduction, by base hydrolysis such as a combination of potassium carbonate, methanol and tetrahydrofuran or by acid hydrolysis such as with hydrochloric acid. In the latter case, the hydrochloride salt is obtained.

The 3-hydroxy- $\Delta^5$ -compound obtained above can optionally be converted to the corresponding 3-keto- $\Delta^4$ -compound by an Oppenauer oxidation using aluminum isopropoxide.

The imine starting material used in this process can be obtained by the reaction of dehydroepiandrosterone with the appropriate cyclopropylamine in refluxing methanol. The reaction is carried out in the presence of a dehydrating agent to remove water from the reaction mixture as it is formed.

When the reduction referred to initially is carried out on an enamine, borane or a borohydride reducing agent such as sodium borohydride is used as the reducing agent. The necessary enamine starting material is obtained by the condensation of dehydroepiandrosterone with an appropriate secondary amine such as dicyclopropylamine. The alcohol final product obtained in this process can be acylated with an appropriate anhydride, such as acetic anhydride, to give the corresponding 3-acetoxy compound or it can be oxidized in an Oppenauer oxidation to give the corresponding 3-keto- $\Delta^4$ -compound.

The present compounds are useful as inhibitors of steroid C<sub>17</sub> 20 lyase and thus inhibit testosterone formation. Consequently, they are useful for treating various androgen-dependent disorders. The present invention thus also encompasses a method for treating androgen-dependent disorders which comprises administering to an individual suffering from such a disorder an effective amount of a compound of the present invention. More particularly, the present compounds are useful in the treatment of prostatic carcinoma, benign prostatic hyperplasia and virilism and hirsutism (in women).

It is well established that reduction of serum testosterone levels is useful in the treatment of many cases of prostatic carcinoma. In clinical practice, this has been accomplished by orchiectomy or by diethylstilbestrol treatment but the first approach is often psychologically unacceptable while a number of side effects are associated with the second approach. Thus, an alternative approach to testosterone reduction is desirable and this can be accomplished by the administration of the present compounds. To the extent that prostatic carcinoma is androgen-dependent, the present compounds would block the source of androgens and thus serve as an appropriate treatment for this condition.

The activity of the present compounds as inhibitors of steroid C<sub>17</sub> 20 lyase was established using microsomal preparations of the steroid C<sub>17</sub> 20 lyase enzyme from human or laboratory animal testis; human testes used for this purpose were obtained from therapeutic orchiectomies. The enzyme was incubated with NADPH and the test compound in the concentration range  $5 \times 10^{-3}$  M to  $3 \times 10^{-5}$  M and the extent of inhibition of the enzyme was determined with time-dependency of inhibition being established by a decline in enzyme activity with the time of exposure to the test compound. Time-dependency of inhibition often

implies irreversible inactivation of the enzyme and irreversibility was specifically established by inability to restore enzyme activity by dialysis under conditions which maintained activity of native enzyme. When tested according to the above procedure using human enzyme, the compounds of the present invention were found to inhibit the enzyme in a time-dependent manner and irreversibly.

5 In the treatment of the various androgen-dependent disorders described earlier, the compounds of the present invention may be administered orally to the patient being treated to achieve the particular effect desired. The amount of compound to be administered will vary over a wide range and can be any effective amount. Depending on the patient to be treated, and the severity of the condition being treated, the effective amount of compound administered will vary from about 0.625 to 62.5 mg/kg of body weight per  
10 day and preferably from 5 to 30 mg/kg of body weight per day. Unit dosages for oral administration may contain, for example, from 25 to 500 mg of a compound of the invention. Alternatively, the present compounds can be administered by parenteral routes or by implants.

In practicing the method of this invention, the active ingredient is preferably incorporated in a composition containing a pharmaceutical carrier and from about 5 to about 90% by weight of the  
15 cyclopropylamino steroid or a pharmaceutically-acceptable salt thereof. The term "pharmaceutical carrier" refers to known pharmaceutical excipients useful in formulating pharmaceutically active compounds for internal administration to animals, and which are substantially non-toxic and non-sensitizing under conditions of use. The compositions can be prepared by known techniques for the preparation of tablets or capsules and can contain suitable excipients known to be useful in the preparation of the particular type of  
20 composition desired. Suitable pharmaceutical carriers in formulation techniques are found in standard texts, such as Remingtons Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania.

The following examples are presented to illustrate the present invention but they should not be construed as limiting it in any way.

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#### EXAMPLE 1

To a solution of 21 g of dehydroepiandrosterone in a mixture of 175 ml of cyclopropylamine and 150 ml  
30 of methanol there was added 5 g of molecular sieves. The reaction mixture was refluxed for 48 hours, cooled to room temperature, and filtered through magnesium sulfate. The magnesium sulfate was washed with ethyl acetate and the solvent was removed from the combined filtrates under reduced pressure to give 17-(cyclopropylimino)androst-5-en-3 $\beta$ -ol melting at about 187°C.

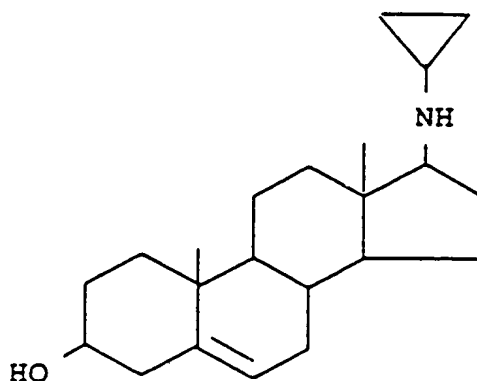
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#### EXAMPLE 2

To a solution of 9.1 g of 17-(cyclopropylimino)androst-5-en-3 $\beta$ -ol in 200 ml of dry ethanol was added 2  
40 g of sodium borohydride. The reaction mixture was stirred at room temperature for 3 hours and then 100 ml of solvent was removed from the mixture under reduced pressure. The reaction mixture was then quenched with dilute acetic acid, diluted with 600 ml of water, and the pH was adjusted to 14 by the addition of sodium hydroxide. The aqueous mixture was extracted 3 times with 600 ml portions of ethyl acetate and the combined organic extracts were dried over magnesium sulfate. Removal of the solvent under reduced  
45 pressure gave the desired 17 $\beta$ -(cyclopropylamino)androst-5-en-3 $\beta$ -ol as a white solid; MS (m/z): 370 (M + 41)<sup>+</sup>, 358 (M + 29)<sup>+</sup>, 330 (M + H)<sup>+</sup>, 312 (MH-H<sub>2</sub>O)<sup>+</sup>. This compound has the following structural formula:

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**EXAMPLE 3**

Reaction of dehydroepiandrosterone with 1-methylcyclopropylamine according to the procedure described in Example 1 gives 17-(1-methylcyclopropylimino)androst-5-en-3 $\beta$ -ol. This is then reduced with sodium borohydride according to the procedure in Example 2 to give 17 $\beta$ -(1-methylcyclopropylamino)androst-5-en-3 $\beta$ -ol.

**EXAMPLE 4**

Reaction of 17-(cyclopropylimino)androst-5-en-3 $\beta$ -ol with an excess of acetic anhydride in the presence of a base (pyridine) followed by removal of the excess anhydride and acetic acid gives 3 $\beta$ -acetoxy-17-(cyclopropylimino)androst-5-ene. Reduction of this ester with sodium borohydride according to the procedure described in Example 2 gives 3 $\beta$ -acetoxy-17 $\beta$ -(cyclopropylamino)androst-5-ene. 3 $\beta$ -(Cyclopentanepropionyloxy)-17 $\beta$ -(cyclopropylamino)androst-5-ene and 3 $\beta$ -(benzenepropionyloxy)-17 $\beta$ -(cyclopropylamino)androst-5-ene are obtained in a similar way using the appropriate acid chlorides.

**EXAMPLE 5**

To a mixture of 10 ml of formic acid and 5 ml of formaldehyde was added 1.4 g of 17 $\beta$ -(cyclopropylamino)androst-5-en-3 $\beta$ -ol. The mixture was heated at reflux for 5 hours, the volume was then reduced to 7.5 ml *in vacuo*, and 10 ml of 50% (w/w) aqueous sodium hydroxide was added. The aqueous layer was separated and extracted with ethyl acetate and the combined organic solutions were dried over magnesium sulfate. The solvent was then removed *in vacuo* and the residual product was purified by flash chromatography to give 17 $\beta$ -[N-methyl(cyclopropylamino)]androst-5-en-3 $\beta$ -ol.

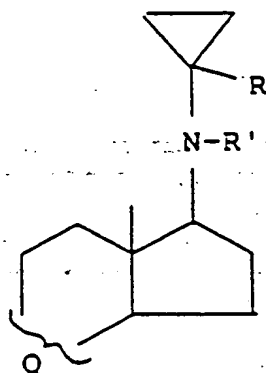
**EXAMPLE 6**

A solution of 1.5 grams of 17 $\beta$ -(cyclopropylamino)androst-5-en-3 $\beta$ -ol in 80 ml of toluene was concentrated to 75% of its original volume and 20 ml of cyclohexanone was added. The mixture was again concentrated to 75% of its volume and 1.5 g of aluminum isopropoxide was added. The reaction mixture was refluxed for 45 minutes, cooled to room temperature, and 50 ml of water and 5 ml of concentrated hydrochloric acid were added. The solution was then treated with 11 g of sodium hydroxide and the two

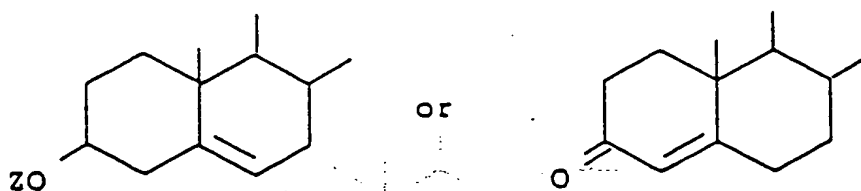
phases were separated. The aqueous phase was extracted with 50 ml of ethyl acetate and the combined organic extracts were dried over sodium sulfate. The solvent was removed *in vacuo* and crystallization of the residue from hexane:ethyl acetate gave 17 $\beta$ -(cyclopropylamino)androst-4-en-3-one. MS (m/z): 327 ( $M^+$ ), 312 ( $M^+ - CH_3$ ).

# Claims

1. A compound of the formula

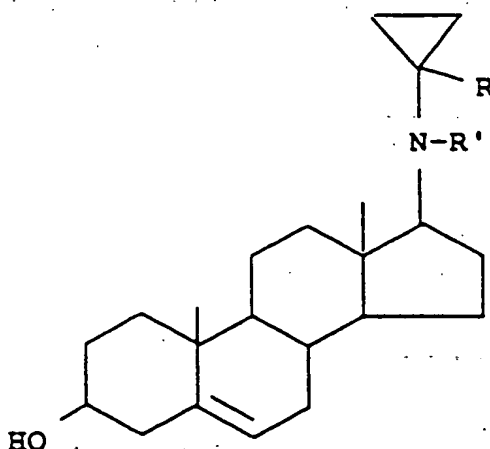


wherein R is hydrogen or methyl; R' is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl or cyclopropyl; and Q is



wherein Z is hydrogen or alkanoyl of 1-10 carbon atoms, or cyclopentane- and benzene-alkanoyl wherein the alkanoyl portion contains up to 4 carbon atoms.

2. A compound according to Claim 1 which has the formula:



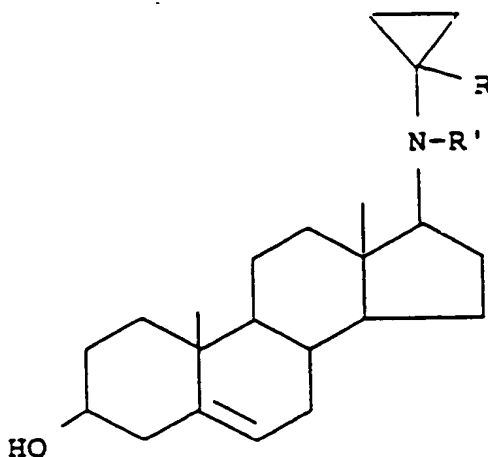
wherein R is hydrogen or methyl; and R' is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl or cyclopropyl.

3. A compound according to Claim 1 which has the formula:

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wherein R is hydrogen or methyl; and R' is hydrogen or C<sub>1-4</sub> alkyl.

4. A compound according to Claim 1 which is 17 $\beta$ -(cyclopropylamino)androst-5-en-3 $\beta$ -ol.
5. A compound according to Claim 1 which is 17 $\beta$ -[N-methyl(cyclopropylamino)]androst-5-en-3 $\beta$ -ol.
6. A compound according to Claim 1 which is 17 $\beta$ -(cyclopropylamino)androst-4-en-3-one.
7. Use of a compound according to any of claims 1 to 6 for the preparation of pharmaceutical drugs for treating androgen-dependent disorders.
8. Pharmaceutical preparations for treating androgen-dependent disorders comprising a pharmaceutical effective amount of a compound according to any of claims 1 to 6 and optionally usual additives and/or carriers.

Claims for the following Contracting State: ES

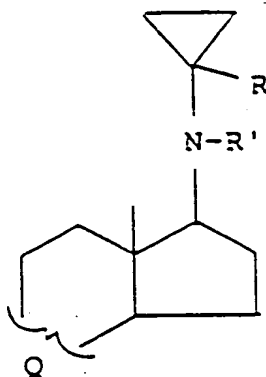
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1. A process for preparing a compound of the formula

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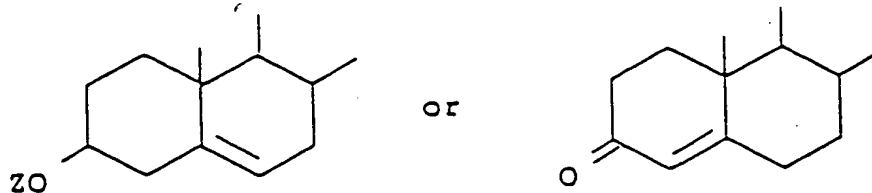
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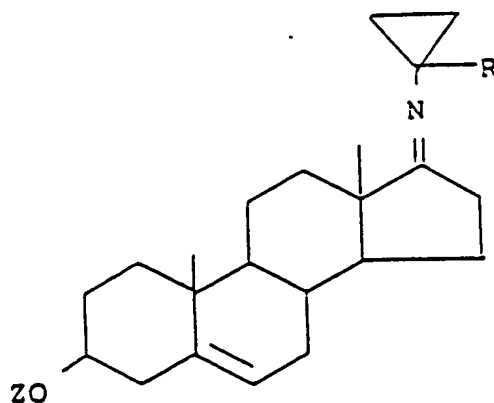
wherein R is hydrogen or methyl; R' is hydrogen, C<sub>1-4</sub> alkyl or cyclopropyl; and Q is

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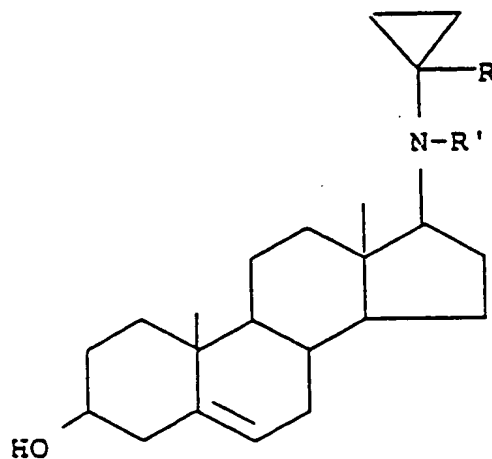


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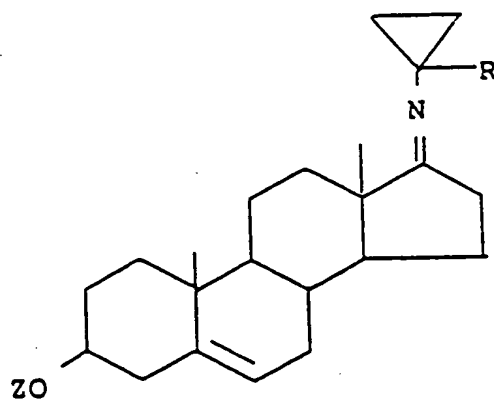
wherein Z is hydrogen or alkanoyl of 1-10 carbon atoms, or cyclopentane- and benzene-alkanoyl wherein the alkanoyl portion contains up to 4 carbon atoms, which comprises reacting an imine of the formula



- 15 wherein R and Z are defined as above, with a hydride reducing agent optionally followed by:
- (a) Reaction with formaldehyde and formic acid to give the compound in which R' is methyl; or
  - (b) Reaction with a C<sub>2</sub> - 4 alkanoyl chloride to give the corresponding alkanamide followed by reduction with sodium cyanoborohydride to give the compounds in which R' is C<sub>2</sub> - 4 alkyl; or
  - (c) Oppenauer oxidation with aluminum isopropoxide to give the corresponding 3-keto- $\Delta^4$ -compound.
- 20 2. A process according to Claim 1 for preparing a compound of the formula:



wherein R is hydrogen or methyl; and R' is hydrogen or C<sub>1</sub> - 4 alkyl which comprises reacting an imine of the formula



- wherein R and Z are defined as above, with a hydride reducing agent optionally followed by:
- (a) Reaction with formaldehyde and formic acid to give the compound in which R' is methyl; or



(b) Reaction with a  $C_{2-4}$  alkanoyl chloride to give the corresponding alkanamide followed by reduction with sodium cyanoborohydride to give the compounds in which  $R'$  is  $C_{2-4}$  alkyl.

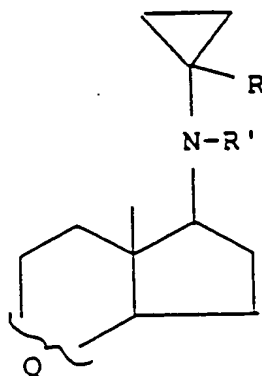
3. A process according to Claim 1 for preparing  $17\beta$ -(cyclopropylamino)androst-5-en-3 $\beta$ -ol which comprises reacting 17-(cyclopropylimino)androst-5-en-3 $\beta$ -ol with sodium borohydride.

4. A process according to Claim 1 for preparing  $17\beta$ -(cyclopropylamino)androst-4-en-3-one which comprises reacting 17-(cyclopropylimino)androst-5-en-3 $\beta$ -ol with sodium borohydride followed by oxidation with aluminum isopropoxide.

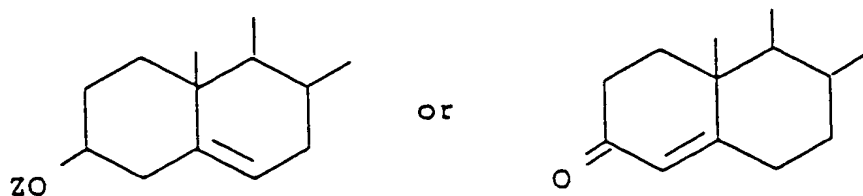
5. Use of the compounds obtainable according to any of claims 1 to 4 for the preparation of drugs for treating androgen-dependent disorders.

Claims for the following Contracting State: GR.

1. A compound of the formula

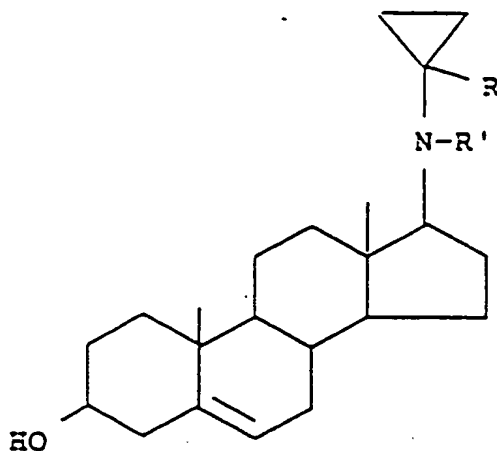


wherein  $R$  is hydrogen or methyl;  $R'$  is hydrogen,  $C_1$ ,  $C_2$  alkyl or cyclopropyl; and  $Q$  is



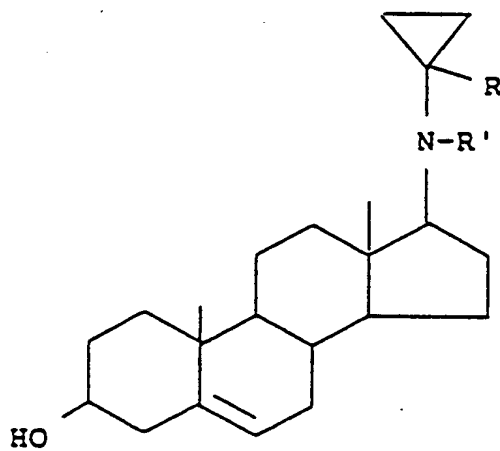
wherein  $Z$  is hydrogen or alkanoyl of 1-10 carbon atoms, or cyclopentane- and benzene-alkanoyl wherein the alkanoyl portion contains up to 4 carbon atoms.

2. A compound according to Claim 1 which has the formula:



wherein R is hydrogen or methyl; and R' is hydrogen, C<sub>1</sub> - C<sub>4</sub> alkyl or cyclopropyl.

3. A compound according to Claim 1 which has the formula:



wherein R is hydrogen or methyl; and R' is hydrogen or C<sub>1</sub> - C<sub>4</sub> alkyl.

4. A compound according to Claim 1 which is 17 $\beta$ -(cyclopropylamino)androst-5-en-3 $\beta$ -ol.

5. A compound according to Claim 1 which is 17 $\beta$ -[N-methyl(cyclopropylamino)]androst-5-en-3 $\beta$ -ol.

6. A compound according to Claim 1 which is 17 $\beta$ -(cyclopropylamino)androst-4-en-3-one.

7. Use of a compound according to any of claims 1 to 6 for the preparation of pharmaceutical drugs for treating androgen-dependent disorders.



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# EUROPEAN SEARCH REPORT

Application Number

EP 88 10 6397

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X	FR-A-1 432 523 (MAY AND BAKER LTD) * Abstract; page 1, lines 19-24 * -----	1-3,8	C 07 J 41/00 A 61 K 31/565
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 J 41/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 21-07-1988	Examiner HENRY J.C.
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ..... & : member of the same patent family, corresponding document			

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